

REMARKS

Reconsideration of this application is respectfully requested. Claims 1-16 and 61-66 were previously under examination in this application. Claims 17-60 and 67 were withdrawn from consideration as being restricted to non-elected inventions. Claims 1-67 have been canceled above. In their place, Applicants have added new claims 68-90 that are in accordance with the previously elected and previously pending claims. No other amendments have been made to this application. Accordingly, new claims 68-90 are presented for further examination on the merits.

New claims 68-90 have been added above. As in the case of the previously pending claims, the new claims are directed to a vector comprising a viral vector, a viral vector nucleic acid or a nucleic acid construct (claims 68-84) and a process for producing the viral vector or viral vector nucleic acid of claim 68 (claims 85-90). In claim 68, the claimed vector is defined as "comprising a viral vector, a viral vector nucleic acid, or a nucleic acid construct that comprises a viral vector nucleic acid sequence." Claim 68 further recites that "said vector, which when introduced into a target cell of interest, expresses an exogenous gene or exogenous nucleic acid sequences, wherein said viral vector nucleic acid comprises at least one non-deletion modification with a non-retroviral sequence leading to an alteration or enhancement of viral vector function."

Other embodiments of Applicants' claimed vector include:

comprising one or more native or non-native promoter/enhancer regions which comprise at least one sequence segment (claim 69); and such sequence segment having been modified (claim 70);

further comprising a native or non-native viral vector terminator or processing signal or segment thereof, or both (claim 71); such having been modified (claim 72); such including a polyadenylation signal (claim 77); and comprising a segment of said viral vector terminator or a segment of said processing signal, or both (claim 78);

said non-deletion modification comprises

a substitution of a native sequence with a non-retroviral sequence segment (claim 73); the sequence segments not being related to promoter/enhancer sequences of a retrovirus (claim 74); and

a mutation selected from the group consisting of a point mutation, an insertion, a substitution and a combination of any of the foregoing (claim 75);

the viral vector comprising a retrovirus (claim 76);

the function of the one or more promoter/enhancer regions have been reduced, inhibited or eliminated (claim 79); the one or more promoter/enhancer regions produce an RNA lacking a polyadenylation signal (claim 80); the one or more native or non-native promoter/enhancer regions being selected from snRNA, tRNA, rRNA and a combination of any of the foregoing (claim 81); such comprising one or more gene or gene segment sequences of said snRNA, tRNA or rRNA gene or genes (claim 82); and the snRNA being selected from U1, U2, U3, U4, U5, U6, U7, U8, U9, U10, U11 and a combination (claim 82); and

the modification of the vector comprising a substitution or replacement of or addition to said one or more native or non-native promoter/enhancer regions with an exogenous gene or an exogenous nucleic acid sequence (claim 84);

In the process claim defined by claim 85, two steps are again recited: providing the vector of claim 1; and introducing the vector into a packaging cell or a packaging cell line under conditions to produce the viral vector or viral vector nucleic acid.

Other embodiments of process claim 85 include:

carrying out the process steps in which the nucleic acid construct has been modified in a promoter/enhancer region (claim 86); the nucleic acid construct has been modified in a non-native promoter/enhancer region (claim 87);

the nucleic acid construct, when introduced into said packaging cell or or packaging cell line, stably integrates into the genome of the packaging cell or packaging cell line (claim 88); the nucleic acid construct having been

modified by means of an episome (claim 89); and the nucleic acid construct having been modified by means of transient expression (claim 90).

A review of new claims 68-90 shows that much of the subject matter of the previously pending claims have been retained and even repeated in various new claims. For example, new claims 76-83 correspond to former claims 7-14, respectively. Further, new process claims 85-90 largely correspond with minor changes to former claims 61-66, respectively. Similarities abound with other claims. For example, new claims 69-72 follow to some extent elements (i), (ii) and (iii) in former claim 1. New claim 73 is premised on former claim 4 except that the modification is a *non-deletion* modification and the substitution is carried out with a non-retroviral sequence segment. Similarly in the case of new claim 75 that is premised on former claim 6, the modification is a *non-deletion* modification and the mutation includes the same Markush members except for a deletion. Also, new claim 84 is premised on former claim 16 except that *native* promoter/enhancer regions have now been included.

It is believed that the subject matter of new claims 68-90 is fully supported by the original disclosure and comprises subject matter to which Applicants are duly entitled to claim. Entry of new claims 68-90 is respectfully requested.

**Correction of Inventorship**

Applicants acknowledge the Examiner's remarks concerning their previous petition to correct the inventorship by adding two fellow co-inventors. That petition should have been filed under 37 C.F.R. §1.48(b) and not §1.48(b). Except for the lack of written consent of the assignee, the mis-designated petition was believed to be otherwise in conformance with the statutory requirements for amending inventorship. In a sincere effort to resolve this matter, Applicants' attorney has attached a written consent of the assignee, Enzo Therapeutics, Inc., as Exhibit 1. It is respectfully requested that Applicants' previous petition be re-processed under 37 C.F.R. §1.48(b), together with the written consent of the assignee (Exhibit 1).

**Sequence Listing**

Acknowledgement is also made regarding the sequence rules under 37 C.F.R. §§1.821-1.825. In response, Applicants are re-submitting attached as Exhibit 2 herewith an Amendment In Response To June 5, 1998 Office Action Directing Applicants To Comply With The Sequence Rules Under 37 C.F.R. §§1.821-1.825, together with a Declaration Under 37 C.F.R. §1.821(g). Entry of Applicants' Sequence Amendment and §1.821(g) Declaration is respectfully requested.

**Restriction Requirement**

Acknowledgement is made of the Examiner's remarks concerning the restriction requirement in this application having been made final. The non-elected inventions of Groups II and III have already been filed in separate divisional applications.

**Submission of Information Disclosure Statement**

Applicants' undersigned attorney and his paralegal are presently retrieving and assembling art-related documents that may be material to the examination of this application. As soon as all of the art-related documents have been assembled, they will be submitted in the form of an Information Disclosure Statement.

**The First Rejection Under 35 U.S.C. §102(b)**

Claims 1-4, 6-11, 15-16, 61-64 stand rejected under 35 U. S.C. §102(b) as allegedly being anticipated by Smith ["Viral Vectors in Gene Therapy," Ann. Rev. Microbiol. 49:807-838 (1995) or Dougherty et al. ["A promoterless retroviral vector indicates that there are sequences in U3 required for 3' RNA processing," Proc.

Natl. Acad. Sci. (USA) 84:1197-1201 (March 1987). In the Office Action (page 3), the Examiner stated:

Applicants claim viral vectors (i.e. a retrovirus vector) capable of expressing a foreign nucleic acid sequence, said vectors comprising a modified native promoter/enhancer, a non-native promoter's gene or gene segment, a native or non-native viral vector terminator, two or more modified segments and a process for producing said vectors comprising introducing the vectors into a packaging cell.

Smith (Annu. Rev. Microbiol., 1995, Vol. 49, pp. 807-838, see whole article, particularly pp. 810-815 and 817-820) and Dougherty et al. (PNAS, 1987, Vol. 84, pp. 1197-1201, see whole article, particularly Figs. 1-3 and pp. 1198-1199) recite viral vectors (i.e. retroviral or adenoviral vectors) capable of expressing a foreign nucleic acid sequence of interest, said vectors comprising a modified native promoter/enhancer sequence, a non-native promoter's gene or gene segment, a native or non-native viral vector terminator, two or more modified segments, one or more non-native promoters capable of producing an RNA lacking a polyA signal, a process for producing the vectors comprising introducing the vectors into a suitable packaging cell line. Smith and Dougherty et al. therefore anticipate the claimed invention.

The anticipation rejections are respectfully traversed.

With respect to Smith's review article, it is submitted that this document does not anticipate the present invention because no disclosure or suggestion is made that modification to a viral vector can be made by replacement of the viral vector nucleic acid with a non-retroviral sequence, unlike Applicants' claimed invention.

In the case of Dougherty et al., this paper does not anticipate the present invention for the plain and simple fact that the authors merely disclose a deletion of the U3 region containing the LTR promoter. They do not disclose or suggest Applicants' invention wherein a non-deletion modification in the viral vector nucleic acid has been effected with a non-retroviral sequence leading to an alteration or enhancement of viral vector function.

In view of the foregoing remarks and the lack of identity of material elements between either Smith's review article or Dougherty's paper and the instantly claimed invention, Applicants respectfully request reconsideration and withdrawal of the first anticipation rejection.

**The Second Rejection Under 35 U.S.C. §102(b)**

Claim 5 stands rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Smith. In the Office Action (page 4), the Examiner stated:

Applicants claim viral vectors comprising substitution of a native promoter/enhancer with a non-native segment wherein the substituted segment is approximately the same size as the native segment.

Smith recites retroviral vectors containing LTRs from different retroviruses substituted for the native LTR. Since the LTRs from different retroviruses are approximately the same size, it must be assumed that Smith teaches the claimed invention.

The second anticipation rejection is respectfully traversed.

It is submitted that Smith does not disclose or suggest the embodiment of claim 73 wherein the non-deletion modification comprises a substitution of a native sequence segment with a non-retroviral sequence segment. In the case of Smith's review article, any or all substitutions are carried out with retroviral elements.

In light of the foregoing distinction in material elements, reconsideration and withdrawal of the second anticipation rejection is respectfully requested.

**Commonality of Ownership**

Applicants wish to point out that each of the inventions being claimed was commonly owned at the time of their invention.

**The First Rejection Under 35 U.S.C. §103(a)**

Claims 12 and 14 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Smith in view of Thompson et al. [U.S. Patent No. 5,750,390, filed on August 26, 1992]. In the Office Action (page 5), the Examiner stated:

Applicants recite viral vectors comprising an snRNA promoter (i.e. the U6 snRNA promoter). Smith is recited as in the above 35 USC 102(b) rejection of claims 1-4, 6-11, 15-16 and 61-64. Thompson et al. (U.S. Patent #5,750,390, issued 5/12/98, priority back to 8/26/92, see whole document, particularly column 8) recites the well known use of the strong human U6 snRNA promoter in the context of expression vectors.

The ordinary skilled artisan, seeking to choose a promoter for inclusion in an expression vector of the type recited by applicants and Smith, would have been motivated to use the U6 snRNA promoter (as recited by Thompson et al.) because said promoter is a well characterized strong promoter which has been used in prior art expression vectors. It would have been obvious for the ordinary skilled artisan to do this because Thompson et al. Indicates that the human U6 snRNA promoter is a strong, versatile, promoter for use in expression vectors. Given the teachings of the cited prior art, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

The first obviousness rejection is respectfully traversed.

As pointed out above in regard to the two anticipation rejections, there is no disclosure or suggestion in Smith's review article that modification to a viral vector can be made by replacement of the viral vector nucleic acid with a non-retroviral sequence, unlike Applicants' claimed invention. Moreover, Smith does not disclose or suggest Applicants' claimed invention wherein the non-deletion modification comprises a substitution of a native sequence segment with a non-retroviral sequence segment. As pointed out above, any or all substitutions in Smith's review article are carried out with retroviral elements, unlike Applicants' claimed invention. Accordingly, even if it were obvious to use Thompson's U6 snRNA promoter in Smith's retroviral vectors, such a modification would still not reach Applicants' claimed invention for the patentable distinctions described above.

In light of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the first obviousness rejection.

**The Second Rejection Under 35 U.S.C. §103(a)**

Claim 13 stands rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Smith in view of Greatbatch et al. [U.S. Patent No. 5,324,643, filed on July 20, 1991]. In the Office Action (pages 5 and 6), the Examiner stated:

Applicants recite viral vectors comprising a tRNA promoter and the gene or gene segment associated with said promoter.

Smith is applied as in the above 35 USC 102(b) rejection.

Greatbatch et al. (U.S. Patent #5,324,390, issued 6/28/94, see whole document, particularly columns 16-17) teaches the use of a tRNA promoter in the context of a recombinant viral expression vector and teaches that the tRNA gene sequence can be maintained and transcribed and should not interfere with the activity of the heterologous nucleic acid to be expressed by the vector.

The ordinary skilled artisan, seeking to choose a promoter for inclusion in an expression of the type disclosed by Smith or applicants would have been motivated to use the tRNA promoter (and optionally the tRNA gene or segment thereof) because Greatbatch et al. indicates that the tRNA promoter is desirable because of economy and size and because polIII promoters such as the tRNA promoters are more or less universal in expression. It would have been obvious for the skilled artisan to do this because of the well known properties of tRNA promoters (small size, universal expression, etc.) and their use in expression vectors of viral or non-viral character. Given the teachings of the cited prior art, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

The second obviousness rejection is respectfully traversed.

As in the case of the first obviousness rejection, even the inclusion of Greatbatch's patent to Smith's review article would not reach Applicants' claimed invention. Assuming *arguendo* that it would have been obvious to a person of ordinary skill in the art to adopt or modify Smith's retroviral vectors with Greatbatch's tRNA promoters and tRNA gene sequences, such would not have permitted that ordinarily skilled person from reaching Applicants' claimed invention. For reasons discussed *supra*, Smith's review article does not disclose or suggest Applicants' claimed invention wherein the non-deletion modification comprises a substitution of a native sequence segment with a non-retroviral sequence segment. Furthermore, in Smith's review article, any or all substitutions are carried out with retroviral elements, unlike Applicants' claimed invention. Accordingly, combining Greatbatch's patent disclosure with Smith's review article would not have rendered Applicants' claimed invention obvious at the time their invention was made.

It is respectfully requested, therefore, that the second obviousness rejection be withdrawn upon reconsideration.

**The Rejection Under 35 U.S.C. §112, Second Paragraph**

Claims 1-16 and 61-66 stand rejected under 35 U.S.C. §112, second paragraph, for indefiniteness. In the Office Action (pages 7 and 8), the Examiner stated:

[1] Claims 1, 11 and 64 (and dependent claims) are vague in the recitation of the phrases "...said vector being capable of expressing..." or "... promoters are capable of..." or "...construct is capable of stable integration..." because the capacity of a compound or composition to perform some function is merely a statement of a latent characteristic of said compound or composition and said language carries no patentable weight.

[2] Claims 1-16 and 61-66 are vague in the use of terms "native" and "non-native" with regard to promoters or viral vectors or segments because it is unclear as to the context for these terms. For example, viral vectors generally comprise different sequences from various sources, i.e. a vector backbone, a heterologous viral or cellular promoter, a polyA sequence from a different virus, a splice donor site from another different source, etc. The use of the terms "native" and "non-native" in this context carries no meaning since each element of a viral vector could be considered "native" to the vector and every other element could be considered "non-native".

[3] Claims 6, 12 and 14 are vague in that they recite improper Markush language. The members of a Markush group are separated by "and" not "or".

[4] Claims 62 and 63 are vague in that the phrase "wherein said providing step or introducing step" appears unconnected to the following language in the claim.

[5] Claim 65 is unclear because it is unclear how an episome (from any source?) can modify a nucleic acid construct. It is unclear what form of modification is being recited?

[6] Claim 66 is vague because it is unclear what sequence is being transiently expressed?, i.e. some vector sequence or some cellular sequence or a sequence from some other source?

The indefiniteness rejection is respectfully traversed.

In view of the number of points raised in the above rejection, Applicants' attorney has taken the liberty of inserting bold bracketed numbers before each point in order to ensure that each and every point is thoroughly addressed. The remarks below are directed to the six points identified by bold bracketed numbers.

**[1]** Regarding the capability language in former claims 1, 11 and 64, it is believed that the claim language in new claims 68, 80 and 88, corresponding to these former claims, obviates this ground of indefiniteness. New claim 68 recites "[a] vector comprising a viral vector, a viral vector nucleic acid, or a nucleic acid construct that comprises a viral vector nucleic acid sequence, said vector, which when introduced into a target cell of interest, expresses an exogenous gene or exogenous nucleic acid sequences, . . ." New claim 80 depends from claim 69 and it recites "wherein said one or more native or non-native promoter/enhancer regions produce an RNA lacking a polyadenylation signal." Finally, new claim 88 depends from claim 85 and it recites "wherein said nucleic acid construct, when introduced into said packaging cell or packaging cell line, stably integrates into the genome of said packaging cell or said packaging cell line." In view of the presentation of new claims 68, 80 and 88, the first ground of indefiniteness is believed to have been overcome.

**[2]** Regarding the use of the terms "native" and "non-native" applied to various viral vector components, it is believed that both terms are either well defined in the specification or understood by those skilled in the art to which Applicants' invention pertains. For example, it is understood that a "native" component is a component that is a natural component of the virus, and not one that has been otherwise modified, dislocated or artificially introduced into the virus. On the other hand, a "non-native" component is not a natural component of the virus, but rather one that has been modified, or dislocated within the virus, or artificially introduced into the virus. A description of "Non-Native Vector Components" is found in the specification, page 16, second full paragraph. A definition of "Non-Native Component" is also found in the Definitions section of the specification, page 12. In view of the foregoing remarks and cited portions of Applicants' disclosure, it is believed that this ground of rejection for indefiniteness has been overcome.

**[3]** With respect to the improper Markush language in the former claims, it is believed that the presentation of new claims 75, 81 and 83, which correspond to former claims 6, 12 and 14, obviates this ground of indefiniteness.

**[4]** Regarding the lack of connection in the language of former claims 62 and 63, Applicants offer the following remarks. New claim 85 corresponds to former

claim 61 except that its preamble recites "[a] process for producing the viral vector or viral vector nucleic acid or nucleic acid construct that comprises a viral vector nucleic acid sequence of claim 68, said process comprising the steps of . . ." Thus, in new claims 87 and 88 (corresponding to former claims 62 and 63), refer to the nucleic acid construct recited in claim 85 from which claims 87 and 88 both depend. The fact of the matter is that in either the providing step or the introducing step of claim 85, the nucleic acid construct has been modified in a non-native promoter/enhancer region (in the case of claim 87), or stably integrates into the genome of the packaging cell line when introduced therein (in the case of claim 88). It is believed, therefore, that new claims 87 and 88 are sufficiently definite to convey this information to the skilled artisan who is reading the claim language.

[5] Concerning the issue of nucleic acid construct modification by means of an episome, the following remarks are offered in response. This issue was raised in regard to former claim 65, now replaced by new claim 89. As defined in the art, an episome is a genetic element that can exist either free or as part of the normal cellular chromosome. New claim 89 recites "wherein said nucleic acid construct has been modified by means of an episome." It is believed that the claim language at hand is clear and definite in conveying the meaning that the nucleic acid sequence comprising the nucleic acid construct is modified by means of a sequence or sequences found in an episome.

[6] Finally, on the issue of modification of the nucleic acid construct by means of transient expression (this language being found in new claim 90), Applicants wish to point out that transient expression (as opposed to more permanent kinds of gene expression), results from a failure of stable integration and/or a lack of independent replication strategy. Thus, claim 90 is sufficiently clear in reciting an embodiment wherein the nucleic acid sequence contained in a nucleic acid construct is modified in some way (for example, the addition of a sequence) by a transient form of gene expression.

In view of the foregoing remarks and above amendments to the claims, Applicants respectfully request reconsideration and withdrawal of the indefiniteness rejection, thereby placing each of claims 68-90 in an allowable condition.

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Page 16 (Amendment Under 37 C.F.R. § 1.115 – March 15, 1999)

Early and favorable action on this application is respectfully urged.

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**SUMMARY AND CONCLUSIONS**

Claims 68-90 are presented for examination in this application.

This Amendment is accompanied by a Petition Under 37 C.F.R. § 1.137(b) to Revive an Unintentionally Abandoned Application, and authorization for the fee therefor. No other fee or fees, including any claim fees, are believed due in connection with this filing or the accompanying Petition. In the event that any such other fee or fees are due, however, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If it would be helpful to expediting prosecution of this application, Applicants' undersigned attorney may be contacted during normal daytime business hours at (212) 583-0100, or by facsimile, at (212) 583-0150.

Respectfully submitted,



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